PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32680A	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/11351	International filing date *(day/month/year)* 14.10.2003	Priority date *(day/month/year)* 15.10.2002
International Patent Classification (IPC) or both national classification and IPC A61K9/20		
Applicant NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04.05.2004	14.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Luangkhot, N Telephone No. +49 89 2399-7857

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/11351

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-17 as originally filed

Claims, Numbers

1-15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 13 regarding industrial applicability

because:

☒ the said international application, or the said claims Nos. 13 regarding industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	13-15
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-12,14-15
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item I
Basis of the report

1) Although claims 1,2 and 3, directed to a product claim, have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter, namely a composition, and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness. Moreover, lack of clarity of the claims as a whole arises, since the plurality of independent claims makes it difficult, if not impossible, to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the extent of the protection.

Hence, claims 1,2 and 3 do not meet the requirements of Article 6 PCT.

In order to overcome this objection, it would appear appropriate to file an amended set of claims defining the relevant subject-matter in terms of a single claim in each category followed by dependent claims covering features which are merely optional (Rule 6.4 PCT). Applicant should take care however not to add subject-matter which extends beyond the content of the application (Art. 19/34 PCT).

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

2) Claim 13 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3) The documents cited in the International Search Report (ISR) were numbered

respectively from D1-D4; this numbering results from the citation order in the ISR and will be used for the procedure. Unless otherwise specified, the cited passages of each document in the ISR will be considered.

The american publication D3 (US2002/061333) is a family member of the french publication WO0057886 (D2). For clarity purpose only D3 would be commented. Moreover it seems that the compound I of present application is conventionally called deferasirox. Therefore the term deferasirox will be herein used to designate compound I.

4) Novelty and inventive step according to Art. 33(2) and 33(3) PCT

4a) D1 describes the use of deferasirox for the treatment of iron overload induced disease, which can be taken in a unit dose forms such as **dispersible tablets** (see p.7 L.15-31) which **can be prepared by granulating** a mixture obtained by combining the active ingredient with solid carriers, processing the granules after addition of suitable adjuncts to give tablets. D1 discloses a list of **suitable carriers** which are, in particular, fillers, binders, disintegrants, flow-regulating agents or lubricants. These carriers are very well-known in the art.
D1 describes the **benefit of employing dispersible tablets** (see p.8 §2) which is advantageous when the amount of administered active ingredient is "so large that on administration as a tablet which is to be swallowed in undivided form or without chewing that it can no longer be conveniently ingested".
The pharmaceutical preparations contain from **0.1-100% of active ingredient** (see p.7 L.11-13). In particularly D1 discloses oral dosage form such as tablets, capsule and **oral suspension powder**, wherein the quantities of active ingredient amount 200, 300, 400 and 500 mg which correspond to a content of 54-68% (see examples A-D).

The disclosure of D1 anticipates the subject-matter of claim 13 which is not novel (see examples A-D).

4b) The subject-matter of claims 1-12 is novel because none of cited documents describes a **dispersible tablet** comprising deferasirox present in an amount of from **5% to 40%.**

However it does not involve an inventive step in view of D1 taken alone, which describes a tablet which a drug content lying between 54-68%.
In the absence of a surprising/improved effect in view of D1 inventive step cannot be acknowledged because the manufacture of dispersible tablets is within the skill of the expert pharmacist.
It could be argued that D1 fails to mention that the tablet described in example A is dispersible. However in view of the type and amount of the ingredients and of the manufacturing process, it seems that the tablet of D1 is highly likely to be dispersible. The **burden** is on applicant to provide evidence for the inventiveness of the composition as described in claim 1, characterized in that the drug is present in an amount of from **5% to 40%**.

Furthermore the features described in dependent claims 4-12 do not confer inventiveness to present claims 1-3 because the manufacture of dispersible tablets is within the skill of the expert pharmacist. Thus it is matter of routine for the skilled man in the art to find the o**ptimal range or amount of excipients to be used.**
In the absence of a surprising/improved effect inventive step cannot be acknowledged.

4c) The subject-matter of claims 14-15 is not novel in view of D1 because these latter (see Example A) discloses the same manufacturing process as described in claim 1, comprising wet granulation (implicit due to the use of ethanol).

It could be argued that D1 fails to mention that the tablet described in example A is dispersible. However in view of the type and amount of the ingredients and of the manufacturing process, it seems that the tablet of D1 is highly likely to be dispersible. The **burden** is on applicant to provide evidence for the novelty **and** inventiveness of the manufacturing process as described in claim 14.

Even if applicant was able to overcome the novelty objection, he would still have to demonstrate an inventiveness. In the absence of a surprising/improved effect in view of D1 and D3 inventive step cannot be acknowledged because it would be considered as an obvious alternative that the skilled man in the art would routinely performed. The manufacture of dispersible tablets is indeed within the skill of the expert pharmacist.

4d) The dispersible tablet as described in claim 10 does not involve an inventive step because it contains **ingredients that are routinely** used by the skilled man. Moreover as the manufacture of dispersible tablets is within the skill of the expert pharmacist. Thus it is matter of routine for the skilled man in the art to find the **optimal range or amount of excipients to be used.**

In the absence of a surprising/improved effect in view of D1 inventive step cannot be acknowledged.

4e) Moreover claim 10 does not involve an inventive step in view of D1 combined with D3.

D1 describes that dispersible tablet of deferasirox would be advantageous when **large amount** of drug is administered rendering the tablet difficult to swallow.
The difference with the subject-matter of present claim 10 consists in the specific ranges of excipients which are used.
The problem to be solved can be seen as how to provide a dispersible tablet having fast disintegration properties, wherein the **drug is in large amount.**
The solution suggested in present application is to prepare a dispersible tablet with specific amount of excipients.

D3 teaches how to make a dispersible tablet comprising **a large amount of an active ingredient (between 20-60%).** The amount of disintegrants used should lie between **1-25%** (see §18). Other excipients such as microcrystalline cellulose , polysorbate (surfactant), colloidal silica and magnesium stearate are used in an amount which lie within the ranges of claim 10.

Even if D3 does not mention that the dispersible tablet formulation could be applied to deferasirox, the skilled man in the art willing to find a suitable dispersible tablet formulation for a drug, wherein the **drug is present in large content**, will use the formulation of D3 and arrive at the claimed subject-matter of claim 10. Therefore in view of D1 combined with D3, the subject-matter of claim 10 is not inventive.

In the absence of a surprising/improved effect in view of D1 combined with D3

inventive step cannot be acknowledged.

For the regional phase:

5) All terms used throughout the present description and which are registered trade marks, should be identified as such (see guidelines C-II 4.17).

6) For the assessment of the present claim 13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

7) Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application.

The attention of the applicant is drawn to the fact that the application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed.

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT). Preferably these indications should be submitted in handwritten form on a copy of the relevant parts of the application as filed.

8) The applicant is kindly requested to take account of the above objections and give convincing argumentations. The applicant should also indicate in the letter of reply the difference of the subject-matter of the new claim vis-à-vis the state of the art and

the significance thereof.